PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BOREAN PHARMA A/S
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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	24.01.2005
Applicant's or agent's file reference: BOR00005/WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK 03/00735	29.10.2003	29.10.2002

Applicant: BOREAN PHARMA A/S et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BOR00005/WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00735	International filing date *(day/month/year)* 29.10.2003	Priority date *(day/month/year)* 29.10.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/52		
Applicant BOREAN PHARMA A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13.05.2004	24.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Heckl, K Telephone No. +49 89 2399-8430

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00735

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-49 as originally filed

Sequence listings part of the description, Pages

1-37 as originally filed

Claims, Numbers

1-31 as originally filed

Drawings, Sheets

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-3 part,4-21,22,23, 24,25,26-31

   because:

   ☒ the said international application, or the said claims Nos. 24,25 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-3part,22,31 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1part,4-31

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

Re Item II
Priority

The priority documents were not available at the time of establishing this Report. Therefore, it is not at present apparent whether the present application in its essential parts is entitled to the priority claimed. Should the present application in its essential parts not be entitled to the priority claimed, the documents referred to as P/X (see D1-D3 as cited below, Re Item V) in the ISR may become part of the relevant prior art in any regional phase of the present application.

The documents referred to as P/X documents (D1-D3) and as E document (see D6 as cited below, Re Item V) in the ISR claim a priority date before that of the present application. Therefore, they might become relevant in the national phase before the EPO under Art.54(3) and (4) EPC.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Due to the finding that the present application lacks unity of invention, the International Search hae been delimited to subject-matter (i) as identified in the ISR. This s.m. comprises claims 1-3 partially.

Moreover, the ISR has been restricted to "specific binding members" as defined by the examples and the Figures. This concerns claims 1-3, 22 and 31.

Claims 24, 25 and 29 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are referred to in this Report:

D1: WO 03/060072 A (IMMUNEX CORP ;REDDY PRANHITHA (US)) 24 July

2003 (2003-07-24)

D2: WO 03/033720 A (DESJARLAIS JOHN R ;ZALEVSKY JONATHAN (US); FILIKOV ANTON (US); MUC) 24 April 2003 (2003-04-24)

D3: WO 03/057856 A (DESJARLAIS JOHN R ;TANSEY MALU LOURDES G (US); XENCOR (US); DAHIYA) 17 July 2003 (2003-07-17)

D4: BODMER JEAN-LUC ET AL: "The molecular architecture of the TNF superfamily." TRENDS IN BIOCHEMICAL SCIENCES. ENGLAND JAN 2002, vol. 27, no. 1, January 2002 (2002-01), pages 19-26, XP002276709 ISSN: 0968-0004

D5: WO 01/64889 A (XENCOR) 7 September 2001 (2001-09-07)

D6: WO 2004/012673 A (KUAI JUN ;LIN LIH-LING (US); WYETH CORP (US); NICKBARG ELLIOTT (US) 12 February 2004 (2004-02-12)

The prior art:

D1-D3 represent P/X and E documents. These documents will not be considered in this Report (see above, Re Item II).

Documents D4 and D5 represent relevant prior art (see below, Re Item V).

Document D6 represents an E-document. This documents will not be considered in this Report (see above, Re Item II).

Novelty (Art.33(2) PCT):

D4 discloses the molecular architecture of the TNF-superfamily and provides a general overview of the structural features of the TNF-family ligands, and structural features of the TNF receptor family.

D5 relates to non-naturally occurring monomeric TNF-alpha variant proteins which can be used as TNF-alpha antagonists. In particular, D5 aims to treat TNF-alpha related disorders.The monomeric TNF-alpha variant proteins disclosed in D5 are characterized by having at least one amino acid substitution as compared to the wild-type TNF-alpha sequence. The monomeric TNF-alpha variant proteins will, when administered to patient, interact with the wild-type TNF-alpha to form mixed trimers which are incapable of activating receptor signalling (see Fig.1A and 1B of D5)

Considering D4 and D5, the subject-matter of the claims as far as subjected to IPE is

considered novel.

Inventiveness (Art.33(3) PCT):

The prior art discloses several attempts in order to find and develop suitable antagonists for trimeric cytokines, i.e. polypeptides which can bind to the cytokines and sequester the cytokines away from their corresponding receptor and thereby suppress or prevent the activation of the receptor pathway. However, a common technical problem encountered with several of the presently known antagonist products for trimeric cytokines, is that upon formation of an 1:1 complex of the trimeric cytokine and the antagonist, not all the binding sites of the trimeric cytokines are effectively blocked, as at least one of the three receptor bonding sites are left open. The open site(s) may be responsible for initiation of further recruitment of cytokine receptors and - still - be responsible for mediattion of receptor signalling.

This problem is clearly adherent to Eternacept which is a bivalent molecule and which leaves open the third receptor binding site. A similar situation is associated with Infliximab which is a chimeric antibody which also neutralises the biological activity of TNF-alpha, however, leaving two receptor binding sites open.

D5 may be considered closest prior art since. Accordingly, the technical problem to be solved by the present application may be considered as to provide a protein which is capable of forming a 1:1 complex with a trimeric cytokine and at the same time effectively bind all three receptor binding sites of the trimeric cytokine, whereby no receptor binding sites of the trimeric cytokine are left open (see also the present application, page 4, lines 21-28 and page 5, lines 1-8).

As the solution a trimeric polypeptide as claimed in claim 1 is provided. Regarding the cited prior art, it appears that this solution is neither disclosed nor rendered obvious. Therefore, it is also considered inventive.

Certain observations on the international application

The IPEA whishes to add that the above findings would also apply to the claims being dependent on claim 1 as faras s.m. (i) is concerened, including the claims relating to pharmaceutical compositions and to the use thereof in therapy (claims 23-31). However, since no ISR has been drawn up for this s.m., only this hint, but no opinion relating thereto will and can be included into this Report.

The IPEA does not share the opinion of the ISA that the term "specific binding member" lacks clarity and support(Art.6 PCT). This in the light of the disclosure, clarification and exemplification provided in the description, page 8, ll 7-22; page 9, ll 13-20; Table 2; page 11, ll16-31; page 12, ll 22-24.